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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,312	JUNG ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11-13,15 and 16* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11, 12 and 16* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/09 has been entered.

2. Claims 1-9, 11-13, 15 and 16 are all the pending claims for this application.

3. Claim 14 was cancelled and Claims 1, 6 and 11 were amended in the Response of 2/27/09.

4. Claim 15 is withdrawn from examination.

5. Claims 1-9, 11-13 and 16 are all the pending claims under examination.

6. The Office Action contains new grounds for rejection.

Withdrawal of Objections

Drawings

7. The Replacement Sheet containing the corrected drawing figure for Figure 4 was received on 2/27/09. This drawing is accepted by the Examiner.

Claim Objections

8. The objection to Claim 11 is withdrawn in view of the amendment to depend from Claim 1.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, first paragraph

9. The rejection of Claims 1-9, 11, 12, 14 and 16 under 35 U.S.C. 112, first paragraph, because the specification is not enabling for practicing the method in any prokaryotic cell transfected with any expression vector encoding the E-coli heat-stable enterotoxin II signal sequence is withdrawn.

In amending Claim 1 to recite that the transformant is an E. coli bacterium, Applicants have overcome the rejection. Applicants' comments on p. 15 of the Response of 2/27/09 are acknowledged.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

10. The rejection of Claims 1-9, 11, 12, and 16 under 35 U.S.C. 112, first paragraph, is maintained because the specification does not reasonably provide enablement for any Ig constant regions that are just any combinations and any hybrids of IgG, IgA, IgM, IgE, and IgD, *or* just any combinations and any hybrids of IgG1, IgG2, IgG3, IgG4 or CH1, CH2, CH3, CH4 and CL.

The rejection was set forth in the previous Office Action as follows:

"Nature of the Invention/Skill in the Art

Claims 2-7 are interpreted as being drawn to a method of producing an Ig constant region comprising transforming a prokaryotic cell with an expression vector including an E. coli derived signal sequence and a nucleotide sequence encoding an Ig constant region, culturing the transformant and isolating and purifying the Ig constant region where the Ig constant region is IgG, IgA, IgM, IgE, IgD and combinations and hybrids thereof (Claim 2), or IgG1, IgG2, IgG3, IgG4 and combinations and hybrids thereof (Claim 3), or the Ig constant region is an IgG4 constant region (Claim 4) or the Ig constant region is a human aglycosylated IgG4 constant region (Claim 5), or the Ig constant region is one to four domains of CH1, CH2, CH3, CH4 or CL (Claim 6), and the Ig constant region of Claim 6 further comprises a hinge region (Claim 7).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in molecular biology and antibody chemistry.

Disclosure in the Specification

The specification does not provide a sufficient enabling description of the claimed invention. The disclosure appears to show only antibodies with certain specified amino acid substitutions. For example, the specification discloses expression vectors encoding engineered Ig constant domains such as pSTIIGICHI_3, pSTIIdCGIFc, pSTIIdCGISFc, pSTIIdCGISFFc, pSTIIGIMo, pSTIIdCG2Fc, pSTIIdCG4Fc, pSTIIG4CHI_3, pSTIIG4Mo, or pSTIIG4H_K. The instant claims encompass in their breadth any vector encoding any "combinations and hybrids" of a constant region from IgG, IgA, IgM, IgE, or IgD, or of a constant region of IgG1, IgG2, IgG3, IgG4, or of one to four domains of CH1, CH2, CH3, CH4 or CL.

Prior Art Status: Fc modifications

There does not appear to be sufficient guidance in the specification as field as to how the skilled artisan would make and use the claimed "combinations and hybrids thereof" or the "one to four domains…CH1, CH2, CH3, CH4 and CL." The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969) show that even a single amino acid replacement within the CH2 domain of IgG can alter the glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an Fc region of an antibody may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict such "combinations and hybrids thereof" and the combination of which "one to four domains of… CH1, CH2, CH3, CH4 and CL" have the same function as the instant claimed invention. Reasonable correlation must exist between the scope of the claims and scope to enablement set forth. Applicant does not appear to provide guidance as to other "combinations and hybrids thereof" or which if any combination of "one to four domains of… CH1, CH2, CH3, CH4 and CL" can be combined, and that meet all of the claimed limitations.

The specification does not appear to provide sufficient guidance as to which constant domains should or should not be changed to preserve any particular function. The variation permitted by the instant claim language is extensive. There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed such "combinations and hybrids thereof" and the combination of which "one to four domains of… CH1, CH2, CH3, CH4 and CL." The specification provides no direction or guidance regarding how to produce such "combinations and hybrids thereof" and the combination of "one to four domains of… CH1, CH2, CH3, CH4 and CL" as broadly defined by the claims. In view of the lack of guidance in the specification and in view of the

discussion above one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention."

The rejection was maintained in the Office Action of 8/27/08 as follows:

"Applicants allegations on pp. 12-13 of the Response of 5/14/08 and their admissions of record on the bottom of p. 10 of the Response have been considered and are not found persuasive.

Applicants allege that in amending Claim 6 to recite the Ig constant region is composed of one to four domains selected from CH1, CH2, CH3 and CH4 domains overcomes the rejection for this claim; the method is directed to mass expression and purification of Ig constant regions using a heat-stable enterotoxin II signal sequence "*regardless of immunoglobulin function*"; Example 3 shows how to produce dimeric and monomeric Ig constant region constructs; and Example 4 teaches how to express and purify the constructs.

Response to Arguments

Initially, the examiner submits that Applicants are erroneous in asserting or advancing the position- that they are not required to demonstrate the production of a functional Ig constant region by the claimed method steps. This is contrary to the statutory requirement under 112, first paragraph, for an enabling use of the method. One of skill in the art would not be enabled to use the immunoglobulin constant regions produced by the method if the embodiments are inoperative. As noted in *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971), if "compositions are in fact useless, appellant's specification cannot have taught how to use them." 439 F.2d at 1243, 169 USPQ at 434."

MPEP 2161 "An invention may be described without the disclosure being enabling (e.g., a chemical compound for which there is no disclosed or apparent method of making), and a disclosure could be enabling without describing the invention (e.g., a specification describing a method of making and using a paint composition made of functionally defined ingredients within broad ranges would be enabling for formulations falling within the description but would not describe any specific formulation). See *In re Armbruster*, 512 F.2d 676, 677, 185 USPQ 152, 153 (CCPA 1975) ("[A] specification which describes' does not necessarily also enable' one skilled in the art to make or use the claimed invention.")."

MPEP 2164.01(b) "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27USPQ2d 1510, 1513 (Fed. Cir. 1993)."

Secondly, Examples 3 and 4 in the specification show how to produce and express a full length IgG4 heavy chain constant region (CH1-hinge-CH2-CH3) under the control of one promoter and a full length light chain constant region (CL) under the control of a separate promoter. The heavy and light chain are taught as forming a dimer or tetramer linked thru free cysteine residues in each chain. Thus the specification is not enabling for producing constructs comprising a) a heavy chain region that comprises a CH1, hinge, CH2, CH3 (or CH4) domains from any combination of different Ig molecules or b) expressing a hybrid heavy chain with any CL chain to form a dimer because cysteine cross-linking is required for dimerization.

Thirdly, Applicants have not addressed the art references cited in the original rejection which teach and recognize that changes in function(s) are predictable by introducing even minor changes to the Fc domains.

The rejection is maintained because Applicants' attorney arguments do not take the place of supplemental evidence showing an enabling use for the full scope of the method claims and the Ig constant regions produced thereby (Arguments of counsel alone are not found to be sufficient in overcoming the enablement rejection (MPEP 2144.03))."

Applicants' allegations on pp. 6- 11 of the Response of 2/27/09 along with the art references and the 1.132 Declaration of Drs. Jung and Kim have been considered and are not found persuasive.

A) Applicants allege the specification in combination with the art and the 1.132 Declaration evidence render the production of "combinations and hybrids" of Ig constant regions to be routine for the ordinary artisan.

The Declaration illustrates the cloning of a hybrid construct of the Ig constant regions from the hinge region and parts of the CH2 region from IgG2, and from the CH2 and CH3 regions of IgG4 (see Item 5 of the Declaration), and soluble expression of the hybrid Ig constant region in E. coli.

Example 4 in the specification describes by working examples for the expression and purification of the Ig constant regions produced by any of the molecular constructs of the invention.

Response to Arguments

Initially the examiner submits that none of the working embodiments for the recombinant Ig constant regions shown in Table 1 (p. 43 of the specification) would provide examples of an enabling disclosure (or motivation) for the ordinary artisan to create Ig constant region "combinations and hybrids" as from any one or more of IgG1, IgG2, IgG3, and IgG4, *or* as between IgA, IgG, IgM, IgE and IgD. All of these examples are derived from the same parent antibody isotype.

Applicants have only now shown for the first time and by submission of the 1.132 Declaration in the Response of 2/27/09, an example of a hybrid Ig constant domain produced by the method. Notably, the data do not show whether the hybrid was operative, e.g., could serve as a carrier to confer serum resistance, or would have any other relevant function. Still further, it is the examiner's opinion that the primers and the

construct design constitute new matter that has not been previously presented in the application. Applicants are welcome to identify original support for the method of making the hybrid in the foreign language priority document. Alternatively, if they cannot find support and wish to have the new experimental data entered, they are welcome to file a C-I-P application. Finally, the Declaration itself is improper under MPEP 602.03 because the document has not been executed by the declarants.

The Declaration has not been entered and the grounds for rejection remain standing.

B) Applicants agree with the Examiner that the Ig constant regions produced by the claimed process should be functional and useful (see the Action, page 8), but submit that such utility is not necessarily related to the Ig constant region's effector functions in the context of an antibody. Instead, this utility may be related to *its function as a carrier of a drug* (see, e.g., page 10, lines 13-15 of the specification). Example 6 in the specification shows molecules may be readily prepared as drug carriers, such as by conjugating them to a suitable drug, and tested for activity by performing routine screening on their pharmacokinetics (e.g., increased half-life).

Response to Arguments

Generic Claim 1 defines the method as using Ig constant regions from any antibody, and in Example 6 an EPO-PEG-Fc conjugate comprising the Ig construct of HM10929 (IgG1 Fc with modified hinge; see Table 1) in Example 4 was tested for its "use" in serum half-life assays. Thus one example of an Ig constant region produced by

the instant claimed method was shown to have a biological activity of conferring serum resistance on the EPO drug.

Additionally, Applicants are incorrect in their understanding of the law for enablement under 35 U.S.C. 112, first paragraph. The specification must be enabling for making and ***using*** the invention. Applicants' assertion that the Ig constant regions are not required to have a function associated within conventional antibody context, but can act as a carrier to confer serum resistance does not satisfy the legal requirement for the myriad Ig constant regions encompassed by the claim scope having any function. A reasonable number of the Ig constant regions generated by the method must have a utility, otherwise what purpose would be served by practicing the method to produce the product?

Under MPEP 2138.05 and *Birmingham v. Randall*, 171 F.2d 957, 80 USPQ 371, 372 (CCPA 1948) "To establish an actual reduction to practice of an invention directed to a method of making a product, it is not enough to show that the method was performed. "[S]uch an invention is not reduced to practice until it is established that the product made by the process is satisfactory, and [ ] this may require successful testing of the product."

The rejection is maintained because Applicants have not met their burden in showing that a reasonable number of the recombinant Ig constant regions much less any "combinations and hybrids thereof" would have any use much less could they be used by the ordinary artisan.

C) Applicants allege "the advanced state of the art at the time of filing demonstrates that to identify related polypeptide variants that retain their functional characteristics is more predictable than to identify those that lose their functional characteristics."

Examples of screening for polypeptide variants may be found in Wan et al. (Mol. Endocrinol. 17:2240-30 (2003)), which describes the process of screening for variants that retained function (binding to a monoclonal antibody) and variants that lost this function. In particular, Wan et al. prepared a library of 5200 random polypeptide variants, without consideration for tolerant or intolerant amino acids, and detected only 125 variants (less than 2.5%) that no longer specifically bound to a specific antibody.

Bowie et al., (Science 247:1306 (1990), page 1306, right hand column, first full paragraph) teach that proteins are "surprisingly tolerant of amino acid substitutions".

Further, according to textbook knowledge in the molecular biology art with respect to polypeptides, such as enzymes for example, "[in] fact, evidence now indicates that amino acid replacements in many parts of a polypeptide chain can occur without seriously modifying catalytic activity" (see Molecular Biology of the Gene, page 227 (James D. Watson et al., ed., The Benjamin/Cummings Publishing Co., (Menlo Park, CA) (4th ed. 1987)).

Response to Arguments

Contrary to Applicants assertion, Wan appears to be non-analogous art to the instant claimed method. See *Ex parte Murphy and Burford* (217 USPQ 479 (BPAI 1982)) stating in part:

> "The determination that a reference is from a nonanalogous art is therefore two fold. First, we decide if the reference is within the field of the inventor's endeavor. If it is not, we proceed to determine whether the reference is reasonably pertinent to the particular problem with which the inventor was involved."

Wan is not considered to meet either criterion under *Murphy*. Wan does not teach or suggest modifying the Mab 263 but instead focused on epitope mapping for the antibody by using PCT mutagenesis of its ligand, ECD of GH receptor. The mention of Wan begs the question of how this relates to generating modified Ig constant regions and which bears no apparent resemblance to the field of epitope mapping. Thus, it is not necessary for the examiner to even address the second prong of *Murphy*.

Bowie does not in any way suggest that just any position in just any protein is tolerant to amino acid modification. The ordinary artisan would be misled by Bowie if they were to base their understanding on Applicants discussion of the reference. Bowies teaches there are constraints on core sequence and states:

"Because core residue positions appear to be extremely important for protein folding or stability, we must understand the factors that dictate whether a given core sequence will be acceptable. In general only hydrophobic or neutral residues are tolerated at buried sites in proteins, undoubtedly because of the large favorable contribution of the hydrophobic effect of protein stability... (p. 1307, Col. 1); and

"With occasional exceptions, the core must remain hydrophobic and maintain a reasonable packing density. However, since the core is composed of side chains that

can assume only a limited number of conformations, efficient packing must be maintained without steric clashes" (p. 1307, Col. 2) and

"The specific pattern of hydrophobic and hydrophilic residues in an amino acid sequence must limit the number of different structures a given sequence can adopt and may indeed define its overall fold" (1309, Col, 1).

Finally, a copy of the cited page from "Molecular Biology of the Gene" does not appear to have been included with the filed response for the examiner's consideration.

D) Applicants rely on case law decision that an Applicant need not test every embodiment of an invention encompassed by a claim and need not describe a large number of examples, particularly when (as here) the level of skill in the art is high, and the teachings of the specification are ample.

Response to Arguments

The specification and the prior art does not identify 1) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of Ig constant regions produced by the method.

This rejection is maintained.

Claim Rejections - 35 USC § 103

11. The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in

view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03) is maintained.

The rejection was set forth in the previous Office Action as follows:

"The interpretation of Claims 1 and 10 is discussed supra. Claim 10 is further drawn to where the signal peptide is penicillinase, Ipp, heat-stable enterotoxin II, LamB, PhoE, PelB, and OmpA, and Claim 11 is drawn to the heat stable enterotoxin signal peptide of SEQ ID NO: 36.

The method claims for producing an Ig constant region from a prokaryotic cell transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide was prima facie obvious at the time of the invention over Capon and Reilly.

The interpretation of Capon is discussed supra [under

Reilly discloses methods of expressing Fc fusion proteins from expression plasmids encoding Fc portions of heavy and light chains from transformed E. coli [0285], where the a recombinant vector comprises a secretion signal sequence component for prokaryotic host cells that do not recognize and process the signal sequences native to the heterologous polypeptides, and the signal sequence is substituted by a prokaryotic signal sequence such as alkaline phosphatase, penicillinase, Ipp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP. Reilly teaches that the signal sequences used in both cistrons of the expression system are STII signal sequences or variants thereof [0122]. Reilly teaches using "the heat-stable enterotoxin II signal sequence (STII) (Picken et al., Infect. Immun. 42:269-275, 1983, and Lee et al., Infect. Immun. 42:264-268, 1983) for the periplasmic secretion of heavy and light chains, and fine control of translation for both chains was achieved with previously described STII signal sequence variants of measured relative translational strengths, which contain silent codon changes in the translation initiation region (TIR) (Simmons and Yansura, Nature Biotechnol. 14:629-634, 1996; Simmons et al., J. Immunol. Methods (2002) 263:133-147)" [0216]. Applicants specification teaches that the native heat-stable enterotoxin (STII) has the sequence of SEQ ID NO:36 (p. 18, lines 8-11), thus by incorporation through reference to Simmons and Yansura (see Table 1, WT SII nucleotide sequence), Reilly teaches the wt heat-stable enterotoxin signal peptide corresponding to SEQ ID NO: 36.

One skilled in the art at the time of the invention would have been motivated to have produced and been reasonably assured of success in having produced the method invention based on the combined disclosure of Capon and Reilly. Both Capon and Reilly expressly teach methods using transformed prokaryotic cells to express an Ig constant region where the transformant is transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide and culturing the cells to express for purification the Ig constant region. Both Capon and Reilly expressly teach bacterial signal sequences, where Reilly more specifically teaches using the E. coli-derived signal sequences alkaline phosphatase, penicillinase, Ipp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP, and more specifically, the wt heat-stable enterotoxin signal peptide of SEQ ID NO:36. Because each of the references appreciates and teaches signal peptides as being critical to the respective host and bacterial signal peptides had been shown by both references to enable the expression of heavy and light chain constant regions in transformed E. coli, one skilled in the art would have found more than sufficient motivation and been reasonably assured of success in having introduced the E. coli-derived signal peptide sequences of Reilly into the method of Capon in order to arrive at the objective of the instant claimed method. For all of the foregoing reasons, the method was prima facie obvious over Capon and Reilly."

The rejection was maintained in the Office Action of 8/27/08 as follows:

"Applicants' allegations on p. 18 of the Response of 5/14/08 have been considered and are not found persuasive. Applicants allege "Applicants describe the surprising and unexpected results of an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form; a protein expression strategy that is much more effective than conventional methods based on secreting proteins into the periplasmic space (see as-filed specification, page 26, line 25 to page 28, line 13). Furthermore, Applicants provide experimental evidence supporting the surprising and unexpected cytoplasmic, water-soluble immunoglobulin constant region protein expression (see, e.g., Example 4 and Figure 1)."

Response to Arguments

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble

form) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993)."

Applicants' allegations on pp. 12-14 of the Response of 2/27/09 have been considered and are not found persuasive. Applicants allege "Capon et al. do not teach an expression vector comprising a heat-stable enterotoxin II signal sequence, let alone do they teach such a vector that expresses an Ig constant region in the cytoplasm in a water soluble form, as recited in the instant claims. Reilly et al. do not remedy the defects of Capon et al., as this reference, describes a prokaryotic expression system for complete antibodies (see abstract), as opposed to the Ig constant regions of the present invention; and Reilly teaches the vector is used for periplasmic secretion of heavy and light chains. In contrast, the instant claims recite an Ig constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form.

Response to Arguments

The examiner submits that the claims are not in any way limited to an expression vector including a nucleic acid sequence consisting of only the E. coli-derived heat stable enterotoxin II signal sequence and the constant region (Fc) from an immunoglobulin . The claims recite comprising language, thus the claims do not exclude the nucleic acid from including a full length heavy chain and a full length light chain so long as the nucleic acid comprises "an immunoglobulin constant region." Thus, at least with respect to Capon and Reilly, the claimed method encompasses full length antibodies.

Applicants would urge the Office to believe that amending the claims to require that the protein is expressed in the cytoplasm of the bacterium would remove the invention from Reilly. However, as noted previously, Reilly already teaches the E. coli heat-stable enterotoxin II signal peptide corresponding to SEQ ID NO: 36 of instant Claim 11 for use in expression antibodies in E. coli in view of Capon. Therefore, it is the Examiner's position that the signal peptide would behave in an inherently similar manner of processing the antibody protein for expression in the cytoplasm rather then the periplasm. Applicants have not distinguished how their signal peptide of SEQ ID NO:36 would differ in its structure and function from the same signal peptide disclosed in Reilly.

Applicants argue unexpected results using the instant claimed signal peptides in order to achieve cytoplasmic expression in water soluble form, however, Reilly discloses using the same signal peptide of SEQ ID NO:36, therefore, it is not clear how the claimed signal peptides, at least according to SEQ ID NO: 36, are distinguishable over Reilly. It would seemingly be an inherent feature of Reilly's signal peptide to result in expressing proteins in the cytoplasm of bacteria. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product and method are different from those taught by the prior art and to establish patentable differences. (See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989)).

12. The rejection of Claims 1 and 11 under 35 U.S.C. 103(a) as being unpatentable over Capon et al. (US 20030104535; published June 5, 2003; filed May 28, 2002) in view of Reilly et al. (US20050048572; published March 3, 2005; filed 10/30/03) as applied to claims 1 and 11 above, and further in view of Kwon et al. (USPN 6605697; published 8/12/03; filed 6/14/01) is maintained.

The rejection was set forth in the previous Office Action as follows:

"The interpretation of Claims 1 and 10 is discussed supra. Claim 11 is drawn to the heat stable enterotoxin signal peptide of SEQ ID NOS: 36-46.

The method claims for producing an Ig constant region from a prokaryotic cell transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide comprising a heat-stable enterotoxin signal peptide was prima facie obvious at the time of the invention over Capon and Reilly in view of Kwon.

The interpretation of Capon and Reilly is discussed supra.

Kwon discloses expression of fusion proteins in prokaryotic cells where the fusion protein is encoded by a sequence comprising a bacterial-derived signal peptide, and more especially the heat stable enterotoxin peptides (STII) corresponding to SEQ ID NOS:36-46 of Claim 11 are disclosed. See SEQ ID NOS: 1 and 13-22 of Kwon (Table 2). Kwon teaches that the yield of secreted heterologous protein decreases as the secretory efficiency of the signal peptide becomes low. Therefore, the yield of secreted heterologous proteins may be enhanced by modifying the signal peptide moiety of fusion proteins expressed in host microorganisms.

One skilled in the art at the time of the invention would have been motivated to have produced and been reasonably assured of success in having produced the method invention based on the combined disclosure of Capon, Reilly and Kwon. Both Capon and Reilly expressly teach methods using transformed prokaryotic cells to express an Ig constant region where the transformant is transformed with a nucleotide encoding an Ig constant region and an E. coli-derived signal peptide and culturing the cells to express for purification the Ig constant region. Both Capon and Reilly expressly teach bacterial signal sequences, where Reilly more specifically teaches using the E. coli-derived signal sequences alkaline phosphatase, penicillinase, Ipp, or heat-stable enterotoxin II (STII) leaders, LamB, PhoE, PelB, OmpA and MBP, and more specifically, the wt heat-stable enterotoxin signal peptide of SEQ ID NO:36. Kwon alos teaches using the signal sequence of SEQ ID NO:36 for the wild type heat stable enterotoxin II signal peptide and variants thereof in order to express heterologous fusion proteins in E. coli expression systems. Further because Kwon appreciates the sensitivity of the signal peptide sequence in achieving the stability, e.g., expression of the full length fusion protein in a prokaryotic system and provides examples that are shown to work using various fusion proteins, one skilled in the art would have found more than sufficient motivation to have introduced the heat stable enterotoxin signal peptides of Reilly and Kwon into the method of Capon and Reilly in order to reliably and reproducibly express an Ig constant region from a prokaryotic system. Because each of the references appreciates and teaches bacterial signal peptides as being critical to the respective host, and bacterial signal peptides had been shown by all of the references to enable the expression of fusion proteins, where Capon and Reilly further demonstrate expression of heavy and light chain constant regions in transformed E. coli, one skilled in the art would have found more than sufficient motivation and been reasonably assured of success in having introduced the E. coli-derived signal peptide sequences of Reilly and kwon into the method of Capon in order to arrive at the objective of the instant claimed method. For all of the foregoing reasons, the method was prima facie obvious over Capon and Reilly and Kwon."

The rejection was maintained in the Office Action of 8/27/08 as follows:

"Applicants' allegations on p. 19 of the Response of 5/14/08 have been considered and are not found persuasive. Applicants allege neither of the three references describe the surprising and unexpected results of an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form; a protein expression strategy that is much more effective than conventional methods based on secreting proteins into the periplasmic space.

Response to Arguments
In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an immunoglobulin constant region expressed from a vector comprising a heat-stable enterotoxin II signal sequence that is expressed in the cytoplasm in a water-soluble form) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993)."

Applicants' allegations on pp. 12-14 of the Response of 2/27/09 have been considered and are not found persuasive. See the allegations set forth above under section 11 and further as they apply to Kwon.

Response to Arguments

The examiner incorporates the arguments set forth under section 11 above, and further in view of Kwon who teaches other embodiments for the signal peptide sequence reading on the sequences in Claim 11. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product and method are different from those taught by the prior art and to establish patentable differences. (See *In re Best* 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989)).

Conclusion

13. No claims are allowed.

14. Claim 13 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority